Insulin-Like Growth Factor-I and Insulin Are Associated With the Presence and Advancement of Adenomatous Polyps

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Background & Aims: **Insulin and insulin-like growth factor-I (IGF-I) affect proliferation, differentiation, and apoptosis and are potential risk factors for colorectal cancer (CRC). Visceral obesity, possibly via hyperinsulinemia, has also been linked to CRC risk. We evaluated the relationship of insulin, IGF-I, insulin-like growth factor binding protein (IGFBP) 3, and visceral adipose tissue (VAT) in subjects with adenomatous polyps, the precursor lesion of colorectal cancer.** ***Methods:*** **Participants were asymptomatic subjects who underwent screening flexible sigmoidoscopy (FSG) within the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Subjects underwent single-slice, computerized tomography scanning to measure VAT and serum fasting insulin, IGF-I, and IGFBP-3 measurements.** ***Results:*** **Four hundred fifty-eight subjects were enrolled, of which 202 subjects had an adenoma, 70 of which were an advanced adenoma. IGF-I ($P = .02$), IGF-I/IGFBP-3 ratio ($P = .003$), and insulin ($P = .02$) were significantly increased in subjects with adenomas compared with controls. In an unadjusted logistic regression analysis using sex-specific quartile cut points, subjects in quartile 4 in comparison with quartile 1 of IGF-I (odds ratio [OR] = 1.7; [95% CI: 1.0–2.9], *P*trend = .03), IGF-I/IGFBP-3 ratio (OR = 1.9 [95% CI: 1.1–3.3], *P*trend = .01), and insulin (OR = 2.1 [95% CI: 1.2–3.6], *P*trend = .04) were at increased risk of adenoma. When limiting the case group to advanced adenomas, the effect was more pronounced: IGF-I (OR = 2.8 [95% CI: 1.3–6.2], *P*trend = .006), IGF-I/IGFBP-3 ratio (OR = 2.3, [95% CI: 1.0–5.2], *P*trend = .04), and insulin (OR = 2.3 [95% CI: 1.1–4.9], *P*trend = .14). Visceral adipose tissue was not associated with adenoma risk.** ***Conclusions:*** **Levels of IGF-I, ratio of IGF-I/IGFBP-3, and insulin are associated with adenomas and even more so with advanced adenomas. These data support the hypothesis that insulin and IGF-I may contribute to the development and advancement of adenomatous polyps.**

Environmental risk factors for colorectal cancer (CRC) including fat, fiber, or micronutrient intake do not explain the link between obesity,[1–3] diabetes,[4–6] or physical activity[1,7,8] and CRC risk. An alternative hypothesis that incorporates these factors into a pathophysiologic model for CRC risk uses insulin resistance and hyperinsulinemia to link obesity and CRC risk.[9,10] Support of the "insulin hypothesis" of CRC is provided by in vitro[11–13] and epidemiologic data showing a relationship between diabetes and obesity and especially visceral obesity and CRC.[3,5,6,14] Studies have demonstrated an association between waist circumference or waist-to-hip ratio, surrogate measures of intraabdominal fat or visceral adipose tissue (VAT), and subsequent development of CRC[8,15] and large adenomatous polyps (≥1cm in size).[14] Visceral obesity is strongly associated with increased insulin levels.[16–19] Physical inactivity is associated with an increased amount of visceral adipose tissue[20,21] and has also been linked to increased risk for CRC.[1,7,8]

An association between serum insulin[15] or serum C-peptide and incident CRC[22,23] has also been observed. In the Cardiovascular Health Study cohort, the risk of subsequent colon cancer was 2.0- to 2.6-fold increased in subjects in the highest quartile compared with the lowest in waist circumference, waist to hip ratio, fasting and 2-hour postprandial glucose, and 2-hour postprandial insulin.[15] A biologic basis for a central role for insulin in CRC pathogenesis has been established because insulin and insulin-like growth factors (IGFs) stimulate cell proliferation in the colonic mucosa and in carcinoma cell lines and affect apoptosis.[9,11–13] IGFs and insulin-like growth factor binding proteins (IGFBPs) also have important roles in cell cycle regulation and possess mitogenic and antiapoptotic properties.[24] IGF-I, IGFBP-3, and the ratio of the 2 have been implicated as risk factors for CRC, although not consistently.[25] Because insulin and IGF-I can be measured in blood, these factors could

Abbreviations used in this paper: CRC, colorectal cancer; IGF-I, insulin like growth factor-I; IGFBP-3, insulin-like growth factor binding protein-3; VAT, visceral adipose tissue.

0016-5085/05/$30.00
doi:10.1053/j.gastro.2005.05.051

have public health impact if they were determined to be a risk factor for adenoma or cancer.

The association of insulin and insulin-like growth factor to adenomatous polyps has been examined previously in a limited fashion, in small numbers of patients.[26–28] Because of the growth-promoting effects of insulin and IGFs and their possible association with invasive CRC, it is important to examine the relationship of these factors to adenomatous polyps, the precursor lesion of CRC. We concurrently evaluated the relationship of insulin, IGF-I, IGFBP-3, and VAT in asymptomatic subjects who presented for screening flexible sigmoidoscopy.

Materials and Methods

Population

Subjects in this study are drawn from enrollees, originally recruited through mass mailings, in the intervention arm of the Pittsburgh site of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO), a multicenter, randomized clinical trial evaluating the effect of cancer screening tests on site-specific cancer mortality.[29] Over 154,000 subjects have been enrolled in the PLCO trial nationally, and nearly 17,000 were enrolled in the broader Pittsburgh region between 1993 and 2000. Subjects in the intervention arm of the trial undergo periodic cancer screening tests including chest x-ray, flexible sigmoidoscopy, and, for men, digital rectal exam and PSA and, for women, CA-125 and vaginal ultrasound. Subjects are referred to personal physicians for evaluation of screen-detected abnormalities and tracked to determine the results from subsequent diagnostic workups. Pathologic findings are based on the local, community pathologist's interpretation and not subject to central review. Participants in the PLCO trial met the following eligibility criteria: (1) age 55–74 years; (2) not currently undergoing treatment for cancer except basal cell or squamous cell skin cancer; (3) no known prior cancer of the colon, rectum, prostate, lung, or ovaries; (4) no surgical removal of colon, lung, ovary, or prostate; (5) not participating in another cancer screening or cancer prevention trial; (6) males not taking Proscar in the past 6 months, females not taking Novaldex in the past 6 months; (7) able to provide informed consent; (8) no more than 1 PSA test in the past 3 years (for subjects randomized after April 1995); and (9) no colonoscopy, sigmoidoscopy, or barium enema in the past 3 years (for subjects randomized after April 1995).

Subjects for this substudy underwent a screening flexible sigmoidoscopy as part of the trial and were invited by mail to participate. Subjects with a "polyp" on sigmoidoscopy were preferentially approached (69.2%) in comparison with subjects who had a negative flexible sigmoidoscopy exam (30.8%), to increase the population with an adenoma, but without knowledge of the specific pathologic findings at diagnostic colonoscopy at the time of recruitment. To encourage balance between cases and controls, we randomly selected controls according to sex, age (5-year age blocks), and PLCO recruitment period (3 month blocks) of the cases. Subjects were recruited over a 2-year period between January 1998 and November 1999.

Participants were asked to undergo a single-slice CT scan through the L4-L5 interspace for quantification of visceral adipose tissue and, at a separate visit, a fasting blood draw and subcutaneous adipose tissue aspiration. Case subjects who underwent diagnostic colonoscopy for a polyp found on sigmoidoscopy participated in this study after their diagnostic workup was complete and their polyps had been removed. The median time from polypectomy to blood draw in subjects with adenomas was approximately 1 year. The intended sample size calculated for detecting a difference in visceral adipose tissue between subjects with adenomatous polyps and controls was 450. Overall, 480 of 981 (48.9%) subjects invited by mail agreed to participate. Control subjects included those with nonadenomatous findings on colonoscopy and subjects with a negative screening sigmoidoscopy. Subjects who underwent colonoscopy were characterized on the basis of the most advanced finding and grouped into advanced adenoma, nonadvanced adenoma, and nonadenomatous polyp (eg, hyperplastic polyp) categories. An adenoma was defined as advanced if it contained villous features (villous or tubulovillous), was large ($\geq$1 cm as estimated by the endoscopist), or had severe dysplasia.

To investigate the potential for selection bias created as a consequence of nonparticipation, we compared, among men and women, the age, race, marital status, education, cigarette history, history of diabetes, and body mass index (BMI) of enrolled and nonenrolled individuals. Older men and younger women approached to serve as potential control subjects were more likely to enroll ($P < .05$), but no other factor was associated with differential enrollment.

Measurement of IGF-I, IGFBP-3, and Insulin

The serum was initially frozen at −70°C and shipped in bulk for analysis. Analyses were performed on serum from the first thaw cycle. IGF-I was extracted using acid ethanol cryoprecipitation to remove residual IGFBPs from the serum[30] (http://members.mint.net/ea6bii/rogue/Methods.html). Subsequently, the supernatant was assayed for IGF-I using a polyclonal Ab to IGF-I (Nichols Institute, San Juan Capistrano, CA). IGFBP-3 was analyzed by an immunoradiometric assay (IRMA) methodology (DSL, Webster, TX). All samples were extracted and assayed in duplicate by personnel blinded to their case control status. Each batch of 38 samples was analyzed simultaneously with 2 in-house controls. The interassay coefficient of variation for IGF-I was 7.1% and for IGFBP-3 4.5%. The molar ratio was calculated by multiplying 3.7*IGF-I/IGFBP-3. Fasting insulin was measured via a ^{125}I radioimmunoassay (Linco Research, Inc.), with a coefficient of variation of 2.6%.

Measurement of Visceral Adipose Tissue

Subjects were scanned with a 9800-CT scanner (General Electric, Milwaukee, WI). The L4-L5 interspace was de-

termined by review of the lateral scout film of the lower lumber spine. An axial single slice through the L4-L5 interspace measuring 10-mm thickness was performed at 120 kV(p) and 170 mA with a scanning time of 2 seconds. Abdominal adipose tissue was calculated using commercially available CT software (GE Medical Systems, Milwaukee, WI). Adipose tissue area was determined electronically by setting the region of interest for attenuation values within the range of −190 to −30 Hounsfield units. Small alterations of the Hounsfield unit range do not significantly alter VAT measurements.[31–33] Using the trace function, the boundary separating subcutaneous and visceral fat was defined manually using a cursor, and the intraabdominal VAT area was recorded. Previous investigation has confirmed the reproducibility and repeatability of this technique.[34,35] Retroperitoneal adipose tissue was included in the VAT measurement. Total fat was determined by adding the sum of visceral and subcutaneous adipose tissue.

Statistical Methods

We assessed the statistical significance of observed differences involving continuously distributed variables with the 2-sample *t* test and nonparametric Wilcoxon test. Spearman correlation coefficients were calculated to evaluate associations involving insulin, IGF-I, IGFBP-3, molar ratio of IGF-I/IGFBP-3, and demographic, anthropometric, and fat distribution measurements. A value $P < .05$ was considered statistically significant. To detect nonlinear and dose-response relationships, we used sex-specific cut points based on the entire study group to categorize subjects into quartiles according to hormone measures (IGF-I, IGFBP-3, IGF-I/IGFBP-3 molar ratio, and insulin), BMI, body weight, VAT, subcutaneous (SQ) fat, total abdominal fat, VAT as a percentage of total abdominal fat, and SQ fat as a percentage of total abdominal fat. We examined the case vs control distribution according to blood hormone or body fat distribution quartile. We used unconditional logistic regression to estimate crude and adjusted strengths of association between adenoma status and quartile-based measurements (SAS version 8.01; SAS Institute, Inc., Cary, NC). We used the Wald statistic to assess linear trend in regression models that used quartile-based exposures expressed as an ordinal variable on an integer scale (0 vs 1 vs 2 vs 3).

Results

Enrollment included 480 subjects, 304 men (63.3%) and 176 women (36.7%). Of the 304 men, 277 underwent CT scanning (91.1%), and 295 (97.0%) underwent serum testing. Of the 176 women, 169 underwent CT scanning (96.0%), and 173 (98.3%) underwent serum testing. Of the 480 subjects, 22 were excluded from further analyses because of absence of diagnostic follow-up for the abnormality detected at screening flexible sigmoidoscopy (n = 20) or because of the presence of adenocarcinoma of the colon (n = 2), leaving 458 for study. A breakdown of the demographics; the risk factors for colon adenomas; and the measures of body size, adipose tissue distribution, and insulin and IGF by sex are reported in Table 1. Two hundred two subjects had adenomatous polyps, and 256 did not have adenomas detected: 100 of which had no adenomas detected at diagnostic colonoscopy, and 156 of which had a negative screening flexible sigmoidoscopy. Of those with adenomas, 70 (34.6%) had an advanced adenoma, and 132 (65.3%) had nonadvanced adenomas.

A comparison of adenoma subjects (advanced and nonadvanced) with the nonadenoma control group and an analysis comparing association across all 3 groups are presented in Table 2. The adenoma group had a larger percentage of males (69.3% vs 59.0%, respectively, $P = .03$) and tended to be less educated ($P = .06$). The adenoma group did not significantly differ from the nonadenoma group in prior history of diabetes, aspirin, NSAID, or cigarette use or family history of CRC (Table 2). Subjects with advanced adenoma had a lower prevalence of regular aspirin use over the preceding 12 months compared with the nonadvanced adenoma or to the nonadenoma control group (29% vs 45% and 41%, respectively, $P = .08$). Although the adenoma group had similar weight, height, and BMI to the nonadenoma group, CT scanning showed that the nonadenoma group had more subcutaneous fat ($P = .006$) but a similar amount of visceral fat ($P = .96$). Visceral fat as a percentage of total fat differed across the 3 groups ($P = .005$), with subjects with nonadvanced adenomas having the largest percentage.

Analysis of measures of insulin and IGF across all groups showed that IGF-I levels were increased in subjects with adenomas ($P = .02$) and were highest in the advanced adenoma group, intermediate in the nonadvanced adenoma group, and lowest in the control group (132.3 ± 46.6 ng/mL vs 126.3 ± 48.4 ng/mL vs 117.1 ± 44.6 ng/mL, respectively, $P = .03$). The IGF-I/IGFBP-3 ratio was greater in subjects with adenomas compared with controls ($P = .003$), as were the insulin levels (20.5 vs 19.6 μU/mL, respectively, $P = .02$). Insulin level did not differ between advanced and nonadvanced adenoma subjects ($P = .88$).

Insulin level was not correlated with IGF-I ($r = -0.003$, $P = .94$) nor IGFBP-3 ($r = -0.01$, $P = .81$), but IGF-I was correlated with IGFBP-3 ($r = 0.57$, $P < .0001$). BMI ($r = 0.56$, $P < .0001$) and visceral fat ($r = 0.53$, $P < .0001$) were strongly correlated with insulin level but were not correlated with IGF-I ($r = -.003$, $P = .95$; $r = 0.02$, $P = .61$, respectively) or IGFBP-3 ($r = 0.04$, $P = .45$; $r = -0.02$, $P = .63$), respectively. A

Table 1. Baseline Characteristics of the Sample Population

	Men, N = 291 (%)	Women, N = 167 (%)
Demographics		
Age (*y*), mean ± standard deviation	64.3 ± 5.4	63.7 ± 5.1
Race		
White	279 (96)	158 (95)
Non-white	12 (4)	9 (5)
Education		
Less than high school graduate	23 (8)	4 (2)
High school graduate	152 (52)	110 (66)
College graduate	116 (40)	53 (32)
Risk Factors		
History of colon polyp	20 (7)	14 (8)[a]
History of diabetes	21 (7)	11 (7)
Regular aspirin use	120 (41)	66 (38)
Aspirin use dose intensity among regular users	N = 120	N = 64
1 or more/day	70 (58)	31 (48)
1–4/week	31 (26)	19 (30)
≤3/month	19 (16)	14 (22)
Regular NSAID use	60 (21)	56 (34)
NSAID use dose intensity among regular users	N = 60	N = 56
1 or more/day	23 (38)	16 (29)
1–4/week	15 (25)	23 (41)
≤3/month	22 (37)	17 (30)
Cigarette smoking history		
Never cigarette smoker	95 (33)	102 (61)
Ex-cigarette smoker	145 (50)	48 (29)
Current cigarette smoker	51 (18)	17 (10)
Family history of colorectal cancer	25 (9)	12 (7)
Measures of body size, mean ± standard deviation	N = 266	N = 160
Weight (*lb*)	195.0 ± 32.9	164.6 ± 36.8[b]
Height (*in*)	69.9 ± 2.8	64.4 ± 2.5
BMI (kg/m^2)	28.1 ± 4.4	28.0 ± 6.0[b]
Visceral fat (cm^3)	202.4 ± 92.0	163.4 ± 76.4
Subcutaneous fat (cm^3)	278.9 ± 111.1	387.1 ± 127.6
Total fat (cm^3)	481.3 ± 177.0	550.5 ± 185.4
Visceral fat (%)	41.7 ± 9.5	29.1 ± 7.3
Measures of insulin/IGF, mean ± standard deviation	N = 283	N = 164
IGF-I (*ng/mL*)	129.5 ± 46.1	109.2 ± 43.8
IGFBP-3 (*ng/mL*)	3048.9 ± 692.1[c]	3431.6 ± 661.9
IGF-I/IGFBP-3 ratio	0.156 ± 0.04[c]	0.116 ± 0.033
Insulin (*μU/mL*)	20.9 ± 31.9	18.4 ± 17.6

Note. The values in parenthesis are percentages.
[a]N = 166.
[b]N = 159.
[c]N = 282.

more complete correlation matrix has been previously reported.[19]

The flexible sigmoidoscopy control group was similar to the colonoscopy control group (data not shown), except the former included more never smokers (55% vs 34%, respectively, $P < .001$) and had persons with significantly lower median insulin levels, 13.2 (interquartile range, 9.5–23.2) compared with 15.5 (interquartile range, 11.0–23.2) μU/mL, respectively ($P = .002$). This difference was not attributable to subjects with hyperplastic polyps in the colonoscopy control group because there was no significant difference in insulin level ($P = .57$) or IGF-I level ($P = .27$) within the colonoscopy control group between subjects with or without hyperplastic polyps.

In an unadjusted analysis using sex-specific quartile cut points comparing adenoma with nonadenoma subjects (Table 3), subjects in quartile 4 in comparison with quartile 1 of IGF-I (OR = 1.7 [95% CI: 0.98–2.94], *P*trend = .03), of IGF-I/IGFBP-3 ratio (OR = 1.9 [95% CI: 1.1–3.3], *P*trend = .01), or of insulin (OR = 2.1 [95% CI: 1.2–3.6], *P*trend = .04) had a significantly increased risk of adenoma. An analysis adjusted for age, race, education, history of polyp, aspirin use, NSAID use, smoking, and family history of CRC did not substantively change the results (Tables 3–5). When the case

Table 2. Comparison of Advanced Adenoma, Nonadvanced Adenoma, and Control Subjects

	Advanced adenoma N = 70 (%)	*Nonadvanced adenoma N = 132 (%)*	*Control (Non-Adenoma) N = 256 (%)*	*P* Value[a]	*P* Value[b]
Demographics					
Age (*y*), mean ± standard deviation	64.3 ± 5.4	63.8 ± 5.2	64.3 ± 5.4	.70	.59
Sex					
Male	44 (63)	96 (73)	151 (59)	.03	.03
Female	26 (37)	36 (27)	105 (41)		
Race					
White	69 (99)	128 (97)	240 (94)	.14	.06
Non-white	1 (1)	4 (3)	16 (6)		
Education					
Less than high school graduate	4 (6)	11 (8)	12 (5)	.18	.06
High school graduate	44 (63)	80 (61)	138 (54)		
College graduate	22 (31)	41 (31)	106 (41)		
Risk Factors, N (%)					
History of colon polyp	6 (9)	7 (5)[c]	21 (8)	.55	.48
History of diabetes	4 (6)	6 (5)	22 (9)	.30	.13
Regular aspirin use[d]	20 (29)	59 (45)	105 (41)	.08	.68
Regular NSAID use[d]	14 (20)	34 (26)	68 (27)	.53	.49
Cigarette smoking history					
Never cigarette smoker	26 (37)	51 (39)	120 (47)	.03	.16
Ex-cigarette smoker	38 (54)	53 (40)	102 (40)		
Current cigarette smoker	6 (9)	28 (21)	34 (13)		
Family history of colorectal cancer	8 (11)	10 (8)	19 (7)	.54	.56
Measures of body size, mean ± standard deviation	N = 65	N = 126	N = 235		
Weight (*lb*)	177.9 ± 34.3	185.5 ± 34.9	184.2 ± 39.5[e]	.42	.79
Height (*in*)	67.5 ± 3.7	68.4 ± 3.8	67.6 ± 3.8	.07	.12
BMI (kg/m^2)	27.5 ± 4.4	27.8 ± 4.2	28.4 ± 5.6[e]	.56	.36
Visceral fat (cm^3)	171.6 ± 71.1	192.6 ± 90.3	189.6 ± 91.5	.40	.96
Subcutaneous fat (cm^3)	310.2 ± 119.0	299.4 ± 135.0	332.9 ± 126.5	.01	.006
Total fat (cm^3)	481.8 ± 162.8	472.0 ± 194.0	522.5 ± 181.6	.01	.03
Visceral fat (%)	35.9 ± 10.0	39.4 ± 10.6	36.0 ± 10.7	.005	.02
Measures of Insulin/IGF	N = 69	N = 126	N = 252		
IGF-1 (*ng/mL*)	132.3 ± 46.6	126.3 ± 48.4	117.1 ± 44.6	.03	.02
IGFBP-3 (*ng/mL*)	3294 ± 735[f]	3155 ± 709	3179 ± 695	.46	.81
IGF-1/IGFBP3 ratio	0.148 ± 0.042[f]	0.147 ± 0.037	0.136 ± 0.043	.01	.003
Insulin (*μU/mL*)	18.5 ± 10.5	21.5 ± 20.2	19.6 ± 33.4	.08	.02

[a]*P* value comparing adenoma (advanced plus nonadvanced) to control subjects.
[b]*P* value for association across all 3 groups, using χ^2 and Kruskal–Wallis test for categoric and continuous measures, respectively.
[c]N = 131.
[d]Defined as ≥3/month over preceding 12 months.
[e]N = 234.
[f]N = 68.

group was restricted to advanced adenomas, in either an unadjusted or adjusted analysis, the effect was more pronounced: Subjects in quartile 4 relative to quartile 1 of IGF-I (OR = 2.8 [95% CI: 1.3–6.2], *P*trend = .006), IGF-I/IGFBP-3 ratio (OR = 2.3 [95% CI: 1.0–5.2], *P*trend = .04), or insulin (OR = 2.3 [95% CI: 1.1–4.9], *P*trend = .14) had an increased risk of advanced adenoma relative to controls (Table 4). Comparison of the nonadvanced adenoma group with the control group did not demonstrate an association with IGF-I (Table 5), but there was a significant increased risk of nonadvanced adenoma in subjects in quartile 4 of insulin level in comparison with quartile 1 (OR = 2.0 [95% CI: 1.0–3.7], *P*trend = .07) (Table 5). Additional adjustments for BMI, percentage of visceral fat, or insulin or IGF-I did not change the relationship between insulin or IGF-I and adenomas, nor did exclusion of diabetics, or mutual adjustment of IGF-I and IGFBP-3 or mutual adjustment of insulin and IGF-I.

The combination of a jointly elevated IGF-I and an elevated insulin level is demonstrated in Figure 1. An age-adjusted logistic regression model examining the categoric effect of being in quartile 4 of insulin and IGF-I compared with quartile 1 for each variable demonstrated an OR for adenoma status of 3.8 (95% CI: 0.7–7.0). There was no statistically significant interaction between IGF-I and insulin ($P = .10$, $\chi^2_9 = 14.66$, log likelihood ratio test).

Table 3. Quartile Analysis of Adenoma to Control Subjects

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* trend
BMI (kg/m^2)					
Quartile range					
Men	<25.1	≥25.1, <27.5	≥27.5, <30.6	≥30.6	
Women	<24.3	≥24.3, <27.2	≥27.2, <31.0	≥31.0	
Cases/controls	51/54	46/58	44/59	41/59	
OR (95% CI)[a]	1.00	0.84 (0.49–1.45)	0.79 (0.46–1.36)	0.74 (0.42–1.28)	.27
OR (95% CI)[b]	1.00	0.85 (0.47–1.54)	0.77 (0.42–1.40)	0.64 (0.34–1.19)	.15
Visceral fat (cm^3)					
Quartile range					
Men	<136.6	≥136.6, <187.6	≥187.6, <254.4	≥254.4	
Women	<109.4	≥109.4, <155.0	≥155.0, <206.1	≥206.1	
Cases/controls	50/55	41/62	49/54	42/60	
OR (95% CI)[a]	1.00	0.73 (0.42–1.26)	1.00 (0.58–1.72)	0.77 (0.44–1.33)	.59
OR (95% CI)[b]	1.00	0.83 (0.46–1.52)	0.89 (0.47–1.67)	0.87 (0.47–1.63)	.52
Subcutaneous fat (cm^3)					
Quartile range					
Men	<201.7	≥201.7, <267.1	≥267.1, <336.9	≥336.9	
Women	<295.1	≥295.1, <368.3	≥368.3, <476.9	≥476.9	
Cases/controls	55/47	40/64	44/59	43/61	
OR (95% CI)[a]	1.00	0.53 (0.31–0.93)	0.64 (0.37–1.11)	0.60 (0.35–1.05)	.13
OR (95% CI)[b]	1.00	0.58 (0.32–1.07)	0.75 (0.41–1.40)	0.53 (0.28–0.98)	.16
Total fat (cm^3)					
Quartile range					
Men	<361.0	≥361.0, <468.7	≥468.7, <575.8	≥575.8	
Women	<418.7	≥418.7, <531.4	≥531.4, <680.6	≥680.6	
Cases/controls	53/50	44/59	45/60	40/62	
OR (95% CI)[a]	1.00	0.70 (0.41–1.22)	0.71 (0.41–1.22)	0.61 (0.35–1.06)	.10
OR (95% CI)[b]	1.00	0.77 (0.42–1.41)	0.75 (0.41–1.37)	0.57 (0.30–1.08)	.09
Visceral fat (%)					
Quartile range					
Men	<35.2	≥35.2, <41.9	≥41.9, <48.0	≥48.0	
Women	<24.1	≥2.1, <28.8	≥28.8, <33.8	≥33.8	
Cases/controls	42/63	41/57	53/54	46/57	
OR (95% CI)[a]	1.00	1.08 (0.62–1.89)	1.47 (0.85–2.54)	1.21 (0.70–2.10)	.32
OR (95% CI)[b]	1.00	1.13 (0.61–2.10)	1.37 (0.77–2.45)	1.17 (0.62–2.22)	.37
IGF-I (*ng/mL*)					
Quartile range					
Men	<99	≥99, <125	≥125, <155	≥155	
Women	<80	≥80, <101	≥101, <129	≥129	
Cases/controls	37/63	41/60	48/50	57/57	
OR (95% CI)[a]	1.00	1.16 (0.66–2.05)	1.64 (0.93–2.88)	1.70 (0.98–2.94)	.03
OR (95% CI)[b]	1.00	1.18 (0.64–2.19)	1.59 (0.85–2.97)	1.86 (1.02–3.41)	.03
IGFBP-3 (*ng/mL*)					
Quartile range					
Men	<2548	≥2548, <3074	≥3074, <3497	≥3497	
Women	<2995	≥2995, <3371	≥3371, <3800	≥3800	
Cases/controls	42/58	49/57	44/58	47/57	
OR (95% CI)[a]	1.00	1.19 (0.68–2.06)	1.05 (0.60–1.83)	1.14 (0.65–1.98)	.77
OR (95% CI)[b]	1.00	1.21 (0.66–2.20)	1.12 (0.60–2.05)	1.12 (0.59–2.11)	.81
IGF-I/IGFBP-3 ratio					
Quartile range					
Men	<0.130	≥0.130, <0.152	≥0.152, <0.179	≥0.179	
Women	<0.093	≥0.093, <0.114	≥0.114, <0.138	≥0.138	
Cases/controls	34/64	44/64	52/49	52/53	
OR (95% CI)[a]	1.00	1.29 (0.74–2.28)	2.00 (1.13–3.53)	1.85 (1.05–3.25)	.01
OR (95% CI)[b]	1.00	1.15 (0.61–2.16)	1.91 (1.03–3.53)	1.68 (0.92–3.08)	.04
Insulin ($\mu U/mL$)					
Quartile range					
Men	<10.7	≥10.7, <15.0	≥15.0, <21.5	≥21.5	
Women	<9.9	≥9.9, <13.7	≥13.7, <21.1	≥21.1	
Cases/controls	39/68	50/56	41/61	53/45	
OR (95% CI)[a]	1.00	1.56 (0.90–2.69)	1.17 (0.67–2.05)	2.05 (1.17–3.59)	.04
OR (95% CI)[b]	1.00	1.88 (1.03–3.45)	1.17 (0.64–2.15)	2.11 (1.14–3.92)	.05

[a]Odds ratio relative to quartile 1, unadjusted.

[b]Odds ratio relative to quartile 1, adjusted for age (years, 1 degree of freedom [df], race (1 df), education (2 df), history of polyp (1 df), aspirin use (3 df), NSAID use (3 df), cigarette smoking history (2 df), and family history of colorectal cancer (1 df).

Table 4. Quartile Analysis of Advanced Adenoma to Control Subjects

	Quartile 1	*Quartile 2*	*Quartile 3*	*Quartile 4*	*P* trend
IGF-I					
Quartile range					
Men	<99	≥99, <125	≥125, <155	≥155	
Women	<80	≥80, <101	≥101, <129	≥129	
Cases/controls	11/63	13/60	12/50	28/57	
OR (95% CI)[a]	1.00	1.24 (0.52–2.98)	1.38 (0.56–3.38)	2.81 (1.28–6.16)	.006
OR (95% CI)[b]	1.00	1.40 (0.53–3.72)	1.38 (0.52–3.69)	3.44 (1.37–8.64)	.005
IGFBP-3					
Quartile range					
Men	<2548	≥2548, <3074	≥3074, <3497	≥3497	
Women	<2995	≥2995, <3371	≥3371, <3800	≥3800	
Cases/controls	13/58	12/57	20/58	18/57	
OR (95% CI)[a]	1.00	0.94 (0.40–2.23)	1.54 (0.70–3.38)	1.41 (0.63–3.14)	.24
OR (95% CI)[b]	1.00	0.95 (0.36–2.45)	1.79 (0.76–4.23)	1.30 (0.52–3.23)	.28
IGF-I/IGFBP-3 ratio					
Quartile range					
Men	<0.130	≥0.130, <0.152	≥0.152, <0.179	≥0.179	
Women	<0.093	≥0.093, <0.114	≥0.114, <0.138	≥0.138	
Cases/controls	11/64	16/64	15/49	21/53	
OR (95% CI)[a]	1.00	1.45 (0.63–3.38)	1.78 (0.75–4.22)	2.31 (1.02–5.21)	.04
OR (95% CI)[b]	1.00	1.49 (0.57–3.91)	1.68 (0.63–4.44)	1.85 (0.76–4.51)	.06
Insulin					
Quartile range					
Men	<10.7	≥10.7, <15.0	≥15.0, <21.5	≥21.5	
Women	<9.9	≥9.9, <13.7	≥13.7, <21.1	≥21.1	
Cases/controls	14/68	19/56	10/61	21/45	
OR (95% CI)[a]	1.00	1.65 (0.76–3.58)	0.80 (0.33–1.92)	2.27 (1.05–4.92)	.14
OR (95% CI)[b]	1.00	2.45 (1.02–5.89)	0.91 (0.33–2.49)	2.27 (0.95–5.41)	.16

[a]Odds ratio relative to quartile 1, unadjusted.
[b]Odds ratio relative to quartile 1 adjusted for age (years, 1 *df*), race (1 *df*), education (2 *df*), history of polyp (1 *df*), aspirin use (3 *df*), NSAID use (3 *df*), cigarette smoking history (2 *df*), and family history of colorectal cancer (1 *df*).

Discussion

We used a screening population to examine the relationship of insulin, IGF-I, and VAT to adenomatous polyps. We found a statistically significant relationship (odds ratios ranging between 1.7 and 2.1) for IGF-I, IGF-I/IGFBP-3 ratio, and insulin to adenoma status in comparison with nonadenoma controls. This association was more pronounced when limiting the case group to advanced adenomas (odds ratios ranging between 2.3 and 2.8). These results provide support for a relationship between insulin and IGF-I and adenomatous polyps, the precursor to CRC, confirming a link between these analytes and early neoplasia. The stronger association with advanced adenomas is suggestive that insulin and IGF-I may be factors that stimulate nonadvanced adenomas to progress to advanced adenomas. External factors that cause adenomas to develop additional genetic mutations and advance to invasive cancer have not been previously identified. Our study is the largest to date and benefits from utilizing an asymptomatic population, which minimizes selection bias related to clinical factors associated with adenoma detection. Furthermore, it includes a substantial population of advanced adenoma subjects and benefits from concurrent measurement of insulin and IGF and a highly accurate CT scan measurement of adipose tissue distribution. Our study advances the insulin hypothesis of CRC by extending its association to adenomas and by suggesting that these factors may stimulate adenoma progression.

The adenoma-carcinoma sequence, supported by strong circumstantial evidence, has become an accepted paradigm of CRC pathogenesis.[36] According to this hypothesis, CRC begins as a benign adenomatous polyp, and, when accompanied by a progression of genetic mutations in genes such as K-*ras*, the SMAD family, DCC, and p53, some adenomas can advance and become invasive CRC.[37] Although the majority of CRC may evolve through the adenomatous polyp phase, the prevalence of adenomatous polyps exceeds the incidence of CRC. Autopsy studies and studies of screening colonoscopy show that 20%–40% of the population harbor adenomatous polyps,[38,39] which greatly exceeds the 6% lifetime risk of CRC.[40] Little is known about the factors that trigger or advance adenomas to progress to cancer. Study of these factors is difficult because adenomas are removed when they are encountered during the clinical practice of

Table 5. Quartile Analysis of Nonadvanced Adenoma to Control Subjects

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* trend
IGF-I					
Quartile range					
Men	<99	≥99, <125	≥125, <155	≥155	
Women	<80	≥80, <101	≥101, <129	≥129	
Cases/controls	26/63	28/60	36/50	29/57	
OR (95% CI)[a]	1.00	1.13 (0.60–2.15)	1.75 (0.93–3.26)	1.23 (0.65–2.34)	.30
OR (95% CI)[b]	1.00	1.10 (0.54–2.22)	1.65 (0.81–3.35)	1.28 (0.63–2.61)	.33
IGFBP-3					
Quartile range					
Men	<2548	≥2548, <3074	≥3074, <3497	≥3497	
Women	<2995	≥2995, <3371	≥3371, <3800	≥3800	
Cases/controls	29/58	37/57	24/58	29/57	
OR (95% CI)[a]	1.00	1.30 (0.71–2.39)	0.83 (0.43–1.59)	1.02 (0.54–1.91)	.69
OR (95% CI)[b]	1.00	1.42 (0.72–2.80)	0.78 (0.37–1.62)	1.16 (0.55–2.45)	.72
IGF-I/IGFBP-3 ratio					
Quartile range					
Men	<0.130	≥0.130, <0.152	≥0.152, <0.179	≥0.179	
Women	<0.093	≥0.093, <0.114	≥0.114, <0.138	≥0.138	
Cases/controls	23/64	28/64	37/49	31/53	
OR (95% CI)[a]	1.00	1.22 (0.64–2.34)	2.10 (1.11–3.98)	1.63 (0.85–3.12)	.05
OR (95% CI)[b]	1.00	1.08 (0.52–2.22)	2.11 (1.05–4.26)	1.52 (0.75–3.08)	.15
Insulin					
Quartile range					
Men	<10.7	≥10.7, <15.0	≥15.0, <21.5	≥21.5	
Women	<9.9	≥9.9, <13.7	≥13.7, <21.1	≥21.1	
Cases/controls	25/68	31/56	31/61	32/45	
OR (95% CI)[a]	1.00	1.51 (0.80–2.84)	1.38 (0.74–2.60)	1.93 (1.02–3.69)	.07
OR (95% CI)[b]	1.00	1.73 (0.85–3.54)	1.39 (0.71–2.71)	2.04 (0.99–4.21)	.09

[a]Odds ratio relative to quartile 1, unadjusted.
[b]Odds ratio relative to quartile 1, adjusted for age (years, 1 *df*), race (1 *df*), education (2 *df*), history of polyp (1 *df*), aspirin use (3 *df*), NSAID use (3 *df*), cigarette smoking history (2 *df*), and family history of colorectal cancer (1 *df*).

colonoscopy, and thus factors that affect progression cannot be directly observed. Environmental factors are critical to the evolution of adenoma into carcinoma. The rapid increase in CRC incidence and mortality that occurs with migration from a low-incidence region to a high-incidence region points strongly to environmental factors in the etiology of CRC.[41,42] Similarly, dramatic change in CRC mortality within a country over as short a period as a few decades argues against a purely genetic cause and points strongly to the influence of the environment, in conjunction with host genetic susceptibility, on CRC expression.[43,44]

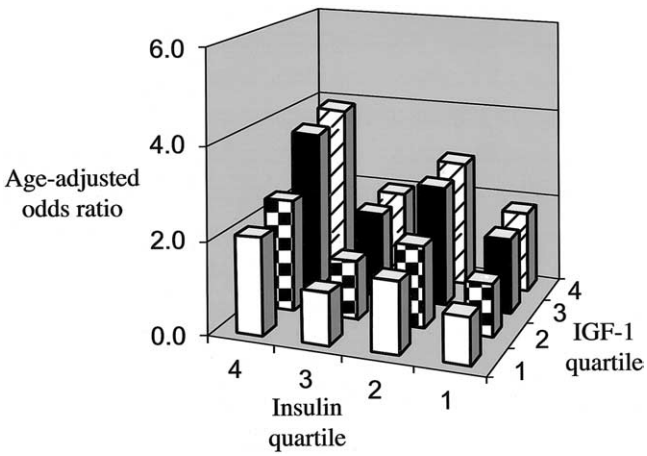

Figure 1. Age-adjusted odds ratio of adenoma risk examining the joint categorical effect of insulin and IGF-I quartile status.

The association of diabetes with CRC is fairly consistent,[4–6] and a recent study demonstrated an increased risk of CRC among subjects with type 2 diabetes on insulin therapy.[45] However, the relationship between IGF-I and CRC is less clear.[25] A nested case control study of men in the Physician's Health Study demonstrated an increased risk of CRC in subjects in the highest quintile of IGF-I (OR = 2.5, *P*trend = .02) and a decreased risk with a higher IGFBP-3 (OR = 0.28, *P*trend = .005).[46] In 2 nested case control studies in women, one showed a relationship between IGF-I and IGFBP-3 and CRC and advanced adenoma, and not with early adenoma,[47] and a second showed no association between IGF-I or IGFBP-3 and CRC.[22] A study in Northern Sweden demonstrated that IGF-I was associated with an increased risk of colon cancer (OR = 2.66, *P*trend = .03) but with a decreased risk of rectal cancer (OR = 0.33, *P*trend = .09).[48] Finally, a recent cohort study in Japanese-American men

in Hawaii showed a general lack of statistical significance between baseline IGF-I or IGFBP-3 and subsequent CRC.[49]

Because 75% of IGF-I is bound to IGFBP-3, and more than 20% is bound to other high-affinity IGFBPs of lower molecular weight, little IGF-I is circulating free. It was initially theorized that the combination of a high circulating level of free IGF-I and/or a low IGFBP-3, such as was observed in the Physician's Health Study, was associated with an increased risk of cancer because of a further increase in free IGF-I. However, IGFBP-3, either through binding IGF-I or by acting through an independent cell surface receptor, can oppose or enhance the biologic action of IGF-I,[50] and thus may have a bidirectional effect on tumor behavior.[25] The lack of association in some studies of IGF-I and IGFBP-3 and CRC is not likely to be due to fluctuating serum levels because studies of the repeatability of IGF demonstrate stability over weeks[51,52] and even over longer durations (1 to 3 years).[22,53] This further suggests that our measurement of IGF-I is a good barometer of IGF-I status in the years preceding the clinical detection of adenomas. Although different assay techniques have been suggested as an explanation for the heterogenous results observed with IGF-I and IGFBP-3 and CRC, when assessed, different assays were highly correlated.[48] A recent meta-analysis of IGF-I and IGFBP-3 and CRC showed only a modest association with IGF-I and no protection with IGFBP-3, and regression models could not confirm a dose-response association of IGF-I and CRC.[25] Thus, the association of IGF-I with CRC has not been consistently observed, but the source of this inconsistency is unclear.

Few studies have examined the relationship of insulin or IGF-I/IGFBP-3 to adenomatous polyps.[26–28] Two small cross-sectional studies provide conflicting evidence on the relation of IGF-I and IGFBP-3 and adenomas, one showing no association[26] and another showing an association with high-risk, advanced adenomas, in comparison with a combined grouping of low-risk adenomas and normal subjects.[27] Our study is the largest and most comprehensive evaluating the relationship between these analytes and adenomatous polyps. Even if subsequent research demonstrates that IGF-I and IGFBP-3 are not associated with CRC, it is possible that IGF-I could impact the development and advancement of adenomas but not necessarily be associated with progression to invasive CRC. This is because, even with advanced adenomas, only a minority progress to invasive cancer.[54] In contrast, insulin may be a growth factor for adenomas and for CRC.

Although insulin and IGFs are often lumped together when considering a possible causal relationship to cancer, the determinants of insulin and IGF-I and IGFBP-3 differ.[19,55] Thus, although considerable data show that insulin levels are strongly influenced by VAT or abdominal obesity, VAT is not associated with IGF-I.[19,56] Similarly, on a biologic basis, the relationship between insulin and IGFs is complex. Insulin can affect the bioactivity of IGF-I by a variety of possible mechanisms, including altering growth hormone receptor levels in the liver[57] and by affecting hepatic IGFBP-1 and IGFBP-2 production.[58] Our data suggest that the effect of insulin and IGF-I on adenoma status is independent of each other. Although our sample size is limited, which incurs a wide confidence interval, examination of the combination of being in the top quartile for both insulin and IGF-I produced a point estimate of a nearly 4-fold increased risk for adenoma. Larger studies are needed to determine more precisely the relationships between insulin, IGF-I, and adenomatous polyps.

Although our findings demonstrate a convincing relationship between insulin and IGF-I and adenomatous polyps, neither VAT nor BMI were associated with adenoma status or advanced adenomas in these data, yet insulin is highly correlated with VAT.[19] A recent small study found no association between VAT and recurrence of adenomatous polyps.[59] Perhaps other factors accompany VAT, which confound its relationship to adenoma status.

Limitations of our investigation should be acknowledged. Dietary and lifestyle factors can affect IGF-I and IGFBP-3 and could have influenced our results. In a recent study in men,[60] high caloric intake was associated with a lower ratio of IGF-I/IGFBP-3. A diet high in protein and minerals has been associated with an increased IGF-I level and to a lesser extent, an increase in the IGF-I/IGFBP-3 ratio.[53] We did not incorporate dietary or physical activity data into our analysis, and physical activity may affect insulin levels. Also, we did not account for glycemic load, which has been associated with CRC in some studies[61] but not others.[62,63] Smoking was not associated with decreased IGF levels in men,[60] although it was in women,[64] but adjustment for smoking did not affect our results. Insulin measurements in this study were fasting, whereas, in the Cardiovascular Health Study, a stronger association with CRC was observed with postprandial as opposed to fasting insulin.[15] However, our design did not allow measurement of a postprandial insulin level. C-peptide, which has a longer half-life than insulin and may correlate to both fasting and nonfasting insulin status[23] has been associated with a 2- to 3-fold increased risk of CRC in prospective studies.[22,23] Sixty percent of our control group did not undergo complete colonoscopy; some of whom could be

misclassified because of the presence of adenomas in the proximal colon. However, there is less than a 3% prevalence of an advanced adenoma in the proximal colon after a negative sigmoidoscopy.[65,66] Because the natural history of adenomas is altered by polypectomy, it will be difficult to determine in a clinical population whether insulin or IGF-I actually cause an adenoma to develop or advance. Our study is a cross-sectional study of prevalent adenomas. We cannot be certain whether insulin or IGF-I causes adenomas to advance or whether adenomas cause insulin or IGF-I to increase. However, blood specimens were collected well after polypectomy, which suggests that insulin and IGF-I affected adenomas, rather than vice versa. Our measurement of IGF-I is likely to be representative of the IGF-I level over the preceding several years,[22] and the stronger association of insulin and IGF-I with advanced adenomas as opposed to nonadvanced adenomas is suggestive that insulin and IGF-I contribute to the growth and progression of adenomatous polyps.[53] Finally, our analysis is based on serum levels, and we cannot account for the autocrine or paracrine production and effect of IGF-I. The serum level may only be an approximation of the tissue or physiologic effect.

In conclusion, insulin, IGF-I, and the ratio of IGF-I/IGFBP-3 are associated with adenomas and even more so with advanced adenomas. These data support the hypothesis that insulin and IGF-I may contribute to the development and advancement of adenomatous polyps.

References

1. Potter JD, Slattery ML, Bostick RM, Gapstur SM. Colon cancer: a review of the epidemiology (review; 304 refs). Epidemiol Rev 1993;15:499–545.
2. Manson JE, Willett WC, Stampfer MJ, Colditz GA, Hunter, DJ, Hankinson SE, Hennekens CH, Speizer FE. Body weight and mortality among women (see comments). N Engl J Med 1995; 333:677–685.
3. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults (comment). N Engl J Med 2003;348:1625–1638.
4. Will JC, Galuska DA, Vinicor F, Calle EE. Colorectal cancer: another complication of diabetes mellitus? Am J Epidemiol 1998; 147:816–825.
5. Hu FB, Manson JE, Liu S, Hunter D, Colditz GA, Michels KB, Speizer FE, Giovannucci E. Prospective study of adult onset diabetes mellitus (type 2) and risk of colorectal cancer in women (comment). J Natl Cancer Inst 1999;91:542–547.
6. La Vecchia C, Negri E, Decarli A, Franceschi S. Diabetes mellitus and colorectal cancer risk. Cancer Epidemiol Biomarkers Prev 1997;6:1007–1010.
7. Lee IM, Paffenbarger RS, Hsieh C. Physical activity and risk of developing colorectal cancer among college alumni. J Natl Cancer Inst 1991;83:1324–1329.
8. Martinez ME, Giovannucci E, Spiegelman D, Hunter DJ, Willett WC, Colditz GA. Leisure-time physical activity, body size, and colon cancer in women. Nurses' Health Study Research Group. J Natl Cancer Inst 1997;89:948–955.
9. Giovannucci E. Insulin and colon cancer (review; 219 refs). Cancer Causes Control 1995;6:164–179.
10. McKeown-Eyssen G. Epidemiology of colorectal cancer revisited: are serum triglycerides and/or plasma glucose associated with risk (review; 148 refs)? Cancer Epidemiol Biomarkers Prev 1994; 3:687–695.
11. Singh P, Rubin N. Insulin like growth factors and binding proteins in colon cancer (review; 190 refs). Gastroenterology 1993;105: 1218–1237.
12. Koohestani N, Tran TT, Lee W, Wolever TM, Bruce WR. Insulin resistance and promotion of aberrant crypt foci in the colons of rats on a high-fat diet. Nutr Cancer 1997;29:69–76.
13. Tran TT, Medline A, Bruce WR. Insulin promotion of colon tumors in rats. Cancer Epidemiol Biomarkers Prev 1996;5:1013–1015.
14. Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer, MJ, Willett WC. Physical activity, obesity, and risk for colon cancer and adenoma in men. Ann Intern Med 1995;122:327–334.
15. Schoen RE, Tangen CM, Kuller LH, Burke GL, Cushman M, Tracy RP, Dobs A, Savage PJ. Increased blood glucose and insulin, body size, and incident colorectal cancer. J Natl Cancer Inst 1999;91:1147–1154.
16. Kissebah AH, Vydelingum N, Murray R, Evans DJ, Hartz AJ, Kalkhoff RK, Adams PW. Relation of body fat distribution to metabolic complications of obesity. J Clin Endocrinol Metab 1982;54:254–260.
17. Bjorntorp P. "Portal" adipose tissue as a generator of risk factors for cardiovascular disease and diabetes. Arteriosclerosis 1990; 10:493–496.
18. Krotkiewski M, Bjorntorp P, Sjostrom L, Smith U. Impact of obesity on metabolism in men and women. Importance of regional adipose tissue distribution. J Clin Invest 1983;72:1150–1162.
19. Schoen RE, Schragin J, Weissfeld JL, Thaete FL, Evans RW, Rosen CJ, Kuller LH. Lack of association between adipose tissue distribution and IGF-1 and IGFBP-3 in men and women. Cancer Epidemiol Biomarkers Prev 2002;11:581–586.
20. Riechman SE, Schoen RE, Weissfeld JL, Thaete FL, Kriska AM. Association of physical activity and visceral adipose tissue in older women and men. Obes Res 2002;10:1065–1073.
21. Ross R. Effects of diet- and exercise-induced weight loss on visceral adipose tissue in men and women (review; 36 refs). Sports Med 1997;24:55–64.
22. Kaaks R, Toniolo P, Akhmedkhanov A, Lukanova A, Biessy C, Dechaud H, Rinaldi S, Zeleniuch-Jacquotte A, Shore RE, Riboli E. Serum C-peptide, insulin-like growth factor (IGF)-I, IGF-binding proteins, and colorectal cancer risk in women. J Natl Cancer Inst 2000;92:1592–1600.
23. Ma J, Giovannucci E, Pollak M, Leavitt A, Tao Y, Gaziano JM, Stampfer MJ. A prospective study of plasma C-peptide and colorectal cancer risk in men. J Natl Cancer Inst 2004;96:546–553.
24. Yu H, Rohan T. Role of the insulin-like growth factor family in cancer development and progression (review; 315 refs). J Natl Cancer Inst 2000;92:1472–1489.
25. Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis (see comment) (review; 60 refs). Lancet 2004;363:1346–1353.
26. Renehan AG, Painter JE, O'Halloran D, Atkin WS, Potten CS, O'Dwyer ST, Shalet SM. Circulating insulin-like growth factor II and colorectal adenomas. J Clin Endocrinol Metab 2000;85: 3402–3408.
27. Renehan AG, Painter JE, Atkin WS, Potten CS, Shalet SM, O'Dwyer ST. High-risk colorectal adenomas and serum insulin-like growth factors. Br J Surg 2001;88:107–113.
28. Teramukai S, Rohan T, Lee KY, Eguchi H, Oda T, Kono S. Insulin-like growth factor (IGF)-I, IGF-binding protein-3 and colorectal

adenomas in Japanese men. Jpn J Cancer Res 2002;93: 1187–1194.
29. Prorok PC, Andriole GL, Bresalier RS, Buys SS, Chia D, Crawford ED, Fogel R, Gelmann EP, Gilbert F, Hasson MA, Hayes RB, Johnson CC, Mandel JS, Oberman A, O'Brien B, Oken MM, Rafla S, Reding D, Rutt W, Weissfeld JL, Yokochi L, Gohagan JK, Prostate Lung Colorectal and Ovarian Cancer Screening Trial Project Team. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Control Clin Trials 2000; 21(Suppl):S309.
30. Grogean T, Vereault D, Millard PS, Kiel D, Maclean D, Orwoll E, Greenspan S, Rosen CJ. A comparative analysis of methods to measure IGF-1 in human serum. Endocr Metab 1997;4:109–114.
31. Kvist H, Sjostrom L, Tylen U. Adipose tissue volume determinations in women by computed tomography: technical considerations. Int J Obes 1986;10:53–67.
32. Borkan GA, Gerzof SG, Robbins AH, Hults DE, Silbert CK, Silbert JE. Assessment of abdominal fat content by computed tomography. Am J Clin Nutr 1982;36:172–177.
33. Rossner S, Bo WJ, Hiltbrandt E, Hinson W, Karstaedt N, Santago P, Sobol WT, Crouse JR. Adipose tissue determinations in cadavers—a comparison between cross-sectional planimetry and computed tomography. Int J Obes 1990;14:893–902.
34. Schoen RE, Thaete FL, Sankey SS, Weissfeld JL, Kuller LH. Sagittal diameter in comparison with single slice CT as a predictor of total visceral adipose tissue volume. Int J Obes Relat Metab Dis 1998;22:338–342.
35. Thaete FL, Colberg SR, Burke T, Kelley DE. Reproducibility of computed tomography measurement of visceral adipose tissue area. Int J Obes Relat Metab Dis 1995;19:464–467.
36. Bond JH. Polyp guideline: diagnosis, treatment, and surveillance for patients with nonfamilial colorectal polyps. The Practice Parameters Committee of the American College of Gastroenterology (published erratum appears in Ann Intern Med 1994;120:347) (review; 90 refs). Ann Intern Med 1993;119:836–843.
37. Terdiman JP. Genomic events in the adenoma to carcinoma sequence. (review; 123 refs). Semin Gastrointest Dis 2000;11: 194–206.
38. Lieberman DA, Weiss DG, Bond JH, Ahnen DJ, Garewal H, Chejfec G. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380 (see comments). N Engl J Med 2000;343:162–168.
39. Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. N Engl J Med 2000;343:169–174.
40. Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, Mariotto A, Feuer EJ, Edwards BK. SEER Cancer Statistics Review, 1975-2001. 2004. Bethesda, MD, National Cancer Institute. Available at: http://seer.cancer.gov/csr/1975_2001/. Accessed October 2004.
41. McMichael AJ, Giles GG. Cancer in migrants to Australia: extending the descriptive epidemiological data. Cancer Res 1988;48: 751–756.
42. Haenszel W. Cancer mortality among the foreign born in the United States. J Natl Cancer Inst 1961;26:37–132.
43. Potter JD. Colorectal cancer: molecules and populations (comment) (review; 238 refs). J Natl Cancer Inst 1999;91:916–932.
44. Svensson E, Grotmol T, Hoff G, Langmark F, Norstein J, Tretli S. Trends in colorectal cancer incidence in Norway by gender and anatomic site: an age-period-cohort analysis. Eur J Cancer Prev 2002;11:489–495.
45. Yang YX, Hennessy S, Lewis JD. Insulin therapy and colorectal cancer risk among type 2 diabetes mellitus patients. Gastroenterology 2004;127:1044–1050.
46. Ma J, Pollak MN, Giovannucci E, Chan JM, Tao Y, Hennekens CH, Stampfer MJ. Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-I and IGF-binding protein-3 (see comments). J Natl Cancer Inst 1999;91: 620–625.
47. Giovannucci E, Pollak MN, Platz EA, Willett WC, Stampfer, MJ, Majeed N, Colditz GA, Speizer FE, Hankinson SE. A prospective study of plasma insulin-like growth factor-1 and binding protein-3 and risk of colorectal neoplasia in women. Cancer Epidemiol Biomarkers Prev 2000;9:345–349.
48. Palmqvist R, Hallmans G, Rinaldi S, Biessy C, Stenling R, Riboli E, Kaaks R. Plasma insulin-like growth factor 1, insulin-like growth factor binding protein 3, and risk of colorectal cancer: a prospective study in northern Sweden. Gut 2002; 50:642–646.
49. Nomura AM, Stemmermann GN, Lee J, Pollak MN. Serum insulin-like growth factor I and subsequent risk of colorectal cancer among Japanese-American Men. Am J Epidemiol 2003; 158:424–431.
50. Jones JI, Clemmons DR. Insulin-like growth factors and their binding proteins: biological actions (review; 345 refs). Endocr Rev 1995;16:3–34.
51. Chan JM, Stampfer MJ, Giovannucci E, Gann PH, Ma J, Wilkinson P, Hennekens CH, Pollak M. Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study (see comments). Science 1998;279:563–566.
52. Goodman-Gruen D, Barrett-Connor E. Epidemiology of insulin-like growth factor-I in elderly men and women. The Rancho Bernardo Study (comment) (erratum appears in Am J Epidemiol 1997;146: 357). Am J Epidemiol 1997;145:970–976.
53. Giovannucci E, Pollak M, Liu Y, Platz EA, Majeed N, Rimm EB, Willett WC. Nutritional predictors of insulin-like growth factor I and their relationships to cancer in men. Cancer Epidemiol Biomarkers Prev 2003;12:84–89.
54. Stryker SJ, Wolff BG, Culp CE, Libbe SD, Ilstrup DM, MacCarty RL. Natural history of untreated colonic polyps. Gastroenterology 1987;93:1009–1013.
55. Kaaks R, Lukanova A. Energy balance and cancer: the role of insulin and insulin-like growth factor-I (review; 236 refs). Proc Nutr Soc 2001;60:91–106.
56. Lukanova A, Soderberg S, Stattin P, Palmqvist R, Lundin E, Biessy C, Rinaldi S, Riboli E, Hallmans G, Kaaks R. Nonlinear relationship of insulin-like growth factor (IGF)-I and IGF-I/IGF-binding protein-3 ratio with indices of adiposity and plasma insulin concentrations (Sweden). Cancer Causes Control 2002;13: 509–516.
57. Tollet P, Enberg B, Mode A. Growth hormone (GH) regulation of cytochrome P-450IIC12, insulin-like growth factor-I (IGF-I), and GH receptor messenger RNA expression in primary rat hepatocytes: a hormonal interplay with insulin, IGF-I, and thyroid hormone. Mol Endocrinol 1990;4:1934–1942.
58. Lee PD, Giudice LC, Conover CA, Powell DR. Insulin-like growth factor binding protein-1: recent findings and new directions (review; 556 refs). Exp Biol Med 1997;216:319–357.
59. Sass DA, Schoen RE, Weissfeld JL, Weissfeld L, Thaete FL, Kuller LH, McAdams M, Lanza E, Schatzkin A. Relationship of visceral adipose tissue to recurrence of adenomatous polyps. Am J Gastroenterol 2004;99:687–693.
60. Chang S, Wu X, Yu H, Spitz MR. Plasma concentrations of insulin-like growth factors among healthy adult men and postmenopausal women: associations with body composition, lifestyle, and reproductive factors. Cancer Epidemiol Biomarkers Prev 2002;11:758–766.
61. Higginbotham S, Zhang ZF, Lee IM, Cook NR, Giovannucci E, Buring JE, Liu S, Women's Health Study. Dietary glycemic load and risk of colorectal cancer in the Women's Health Study. J Natl Cancer Inst 2004;96:229–233.

62. Terry PD, Jain M, Miller AB, Howe GR, Rohan TE. Glycemic load, carbohydrate intake, and risk of colorectal cancer in women: a prospective cohort study. J Natl Cancer Inst 2003; 95:914–916.
63. Oh K, Willett WC, Fuchs CS, Giovannucci EL. Glycemic index, glycemic load, and carbohydrate intake in relation to risk of distal colorectal adenoma in women. Cancer Epidemiol Biomarkers Prev 2004;13:1192–1198.
64. Holmes MD, Pollak MN, Hankinson SE. Lifestyle correlates of plasma insulin-like growth factor I and insulin-like growth factor binding protein 3 concentrations. Cancer Epidemiol Biomarkers Prev 2002;11:862–867.
65. Lewis JD, Ng K, Hung KE, Bilker WB, Berlin JA, Brensinger C, Rustgi AK. Detection of proximal adenomatous polyps with screening sigmoidoscopy: a systematic review and meta-analysis of screening colonoscopy (review; 40 refs). Arch Intern Med 2003;163:413–420.
66. Schoen RE. Prevalence of isolated advanced proximal neoplasia (comment). Arch Intern Med 2003;163:2103–2104.

Received February 2, 2005. Accepted May 11, 2005.

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Supported by grant K07-CA72561 (to R.E.S.) from the National Cancer Institute.